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Total Number of Pages in This Submission

6

Application Number

10/601,861

Filing Date

June 24, 2003

First Named Inventor

Kenneth Walter Locke

Art Unit

1625

Examiner Name

Taylor V. Oh

Attorney Docket Number

215233.00400

### ENCLOSURES (Check all that apply)

<input type="checkbox"/> Fee Transmittal Form	<input type="checkbox"/> Drawing(s)	<input type="checkbox"/> After Allowance Communication to TC
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### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Katten Muchin Rosenman LLP		
Signature			
Printed name	Gilberto M. Villacorta, Ph.D.		
Date	November 1, 2005	Reg. No.	34,038

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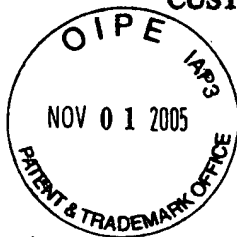
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ATTY. DKT. NO. 215233.00400  
CUSTOMER NO. 27160

PATENT



## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kenneth W. Locke et al.

Examiner: Oh, Taylor V.

Serial No.: 10/601,861

Art Unit: 1625

Filed: June 24, 2003

For: Process for making polymorphic form A of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid

**DECLARATION UNDER 37 C.F.R. §1.132**

Commissioner for Patents  
Washington, DC 20231

Sir:

I, Kenneth W. Locke, Ph.D., hereby make the following declaration:

1. I received a Ph.D. degree in Pharmacology from the Emory University School of Medicine in the year 1985.
2. I have 20 years of experience in the pharmaceutical industry focused primarily on drug discovery and the preclinical and early clinical development of novel therapeutics. Each of the positions described below has provided me with the skills, experience and insight to identify promising drug candidates. My career in the pharmaceutical industry began at Hoechst-Roussel Pharmaceuticals, Inc.,

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heading laboratories for analgesics and anti-inflammatory, and later Alzheimer's disease, drug research. In 1989, I joined Interneuron Pharmaceuticals, Inc., as Manager, Behavioral Neuroscience, taking on positions of increasing responsibility over the next 11 years. Before leaving Interneuron, as Executive Director, Preclinical Development, I was responsible for all aspects of preclinical development for the company's drug portfolio, as well as for in-licensing candidate evaluation. In 2000, I joined Tanabe Research Laboratories U.S.A., Inc., as Vice President of Research, to coordinate the research efforts of chemists and biologists in identifying novel drug development candidates. I am currently employed by MediciNova, Inc., the assignee of the above-referenced patent application, with offices located at 4350 La Jolla Village Drive - Suite 950, San Diego, CA 92122. My current title is Senior Vice President, Portfolio Management.

3. I am named as a co-inventor of the invention claimed in the above-referenced patent application. I have read the contents of the Final Office Action mailed May 19, 2005. I have also been apprised of the Examiner's request, made to assignee's counsel on August 30, 2005, to provide this declaration directed to the superior solubility properties of the claimed orthorhombic crystals of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid (also referred to in the specification of the above-referenced patent application as Form A), as well as the results of certain experiments that are described in Appendix A, attached hereto.

4. As described in the specification of the above-referenced patent application, for example, at page 9, Example 4, the claimed method provides orthorhombic crystals (Form A) that exhibit physical characteristics which are

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different from those displayed by undesired monoclinic crystals. For instance, the desired orthorhombic crystals displayed greater and unexpected solubility compared with the undesired monoclinic crystals of Form B. For example, at 30 °C the solubility of Form B was calculated to be 6.1 g/L, while that of Form A was calculated to be 15.7 g/L – that is, at 30 °C, the claimed orthorhombic crystals displayed more than twice the solubility of the undesired monoclinic crystals. This physical characteristic of greater solubility is also observed at 22 °C and at 40 °C.

5. I would also like to draw the Examiner's attention to Figures 6 and 7 of Appendix A, attached hereto. These figures depict powder x-ray diffraction (PXRD) analyses of tablets made from the claimed orthorhombic crystals and the undesired monoclinic crystals, respectively. As can be readily seen from these figures, the crystalline structure of the two forms, Form A and Form B, are retained in the manufacture of the respective tablets. It is therefore reasonable to assume that the greater solubility characteristics of the claimed orthorhombic crystals are retained in the tablets, which in turn would offer a benefit of greater solubility/bioavailability of active drug to a patient.<sup>1</sup>

6. Other aspects of the Appendix A, which are noteworthy, are Figures 2 and 5. Figure 2 depicts the PXRD analyses for the claimed orthorhombic crystals (Form A) versus undesired monoclinic crystals (Form B or Form C). Note, for example, the three singlet peaks for Form A between about 11.5 and 16.0 (2-Theta scale), whereas Forms B and C (both monoclinic) exhibit three doublet peaks in the same region. Figure 5 depicts differential scanning calorimetry (DSC) thermograms

<sup>1</sup> Dissolution experiments using tablets made from different polymorphic forms of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid were inconclusive because tablets were manufactured with widely different particle sizes for the two polymorphic forms. The particle size used for the manufacture of a tablet

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of Forms A versus B (including tablets made from the two forms). As can be seen from Figure 5, the phase transition for Form A crystals occurs at a lower temperature than Form B crystals. It may be inferred from these results that Form B is the thermodynamically favored crystal structure for this compound.

7. In summary, the claimed method provides orthorhombic crystals which have been shown to exhibit distinct physical and chemical characteristics from the undesired monoclinic forms, including a greater solubility relative to undesired monoclinic crystals.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity or enforceability of any patent maturing from the above-referenced patent application.

Dated: 9/20/05

By: 

Kenneth W. Locke, PH.D.

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from Form A was more than four times the particle size for the manufacture of a tablet from Form B. The dissolution profile of the tablets tested are depicted in Figure 4 of Appendix A, attached hereto.

# A Study of Different Polymorphic Forms of a New Drug Substance, MN-001

Frank Fang<sup>1,2</sup>, Kenneth W. Locke<sup>3</sup>, David Roe<sup>4</sup>, Stebn Petrov<sup>5</sup>, Geoff Carr<sup>1</sup>, Charles Chen<sup>1</sup>  
<sup>1</sup>Pathcon, Inc., <sup>2</sup>To whom correspondence should be addressed (Email: frank.fang@pathcon.com)  
<sup>3</sup>MediNova, Inc., <sup>4</sup>Torcan Chemical Ltd., <sup>5</sup>University of Toronto.

## OBJECTIVE

- Identify NCE MN-001 API polymorphic form
- Develop dissolution test method with discriminative power using four prototypes of 250 mg tablets
- Evaluate the impact of batch-to-batch differences in polymorphic form and particle size of API on the dissolution profile of MN-001 tablets
- Investigate sources of the polymorphic forms of MN-001 within the tablets

## INTRODUCTION

- MN-001 is a new chemical entity with its known polymorphic forms and low intrinsic solubility in water. The chemical structure is shown in Figure 1.
- Pathcon, Inc. is currently being used in clinical trials. Different prototypes of 250 mg tablets using polymorphic form A of API were developed using various formulation processes, such as impurity profile and dissolution rate.
- A leading formulation (NCFN250070) was selected based on stability results, such as impurity profile and dissolution rate.
- The impact of batch-to-batch differences in polymorphic form and particle size of API on the dissolution profile of MN-001 250 mg tablets as well as the nature of the polymorphic forms of MN-001 within the tablets were investigated.

## METHODOLOGY

The dissolution method was developed and validated using USP apparatus 2 at 75 rpm and 900mL of 1% Tween 80 in phosphate buffer at pH=7.4 as dissolution medium. The dissolution profile was determined with sampling time points at 10, 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, 600, 620, 640, 660, 680, 700, 720, 740, 760, 780, 800, 820, 840, 860, 880, 900, 920, 940, 960, 980, 1000, 1020, 1040, 1060, 1080, 1100, 1120, 1140, 1160, 1180, 1200, 1220, 1240, 1260, 1280, 1300, 1320, 1340, 1360, 1380, 1400, 1420, 1440, 1460, 1480, 1500, 1520, 1540, 1560, 1580, 1600, 1620, 1640, 1660, 1680, 1700, 1720, 1740, 1760, 1780, 1800, 1820, 1840, 1860, 1880, 1900, 1920, 1940, 1960, 1980, 2000, 2020, 2040, 2060, 2080, 2100, 2120, 2140, 2160, 2180, 2200, 2220, 2240, 2260, 2280, 2300, 2320, 2340, 2360, 2380, 2400, 2420, 2440, 2460, 2480, 2500, 2520, 2540, 2560, 2580, 2600, 2620, 2640, 2660, 2680, 2700, 2720, 2740, 2760, 2780, 2800, 2820, 2840, 2860, 2880, 2900, 2920, 2940, 2960, 2980, 3000, 3020, 3040, 3060, 3080, 3100, 3120, 3140, 3160, 3180, 3200, 3220, 3240, 3260, 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